body provide them with a source of water. In more humid climates, carpets and couches contain the largest populations because of the constant availability of moist ambient air.

The prevalence of the three major species of mites varies both geographically and between homes in the same geographic area. Most homes are inhabited by more than one species. In coinhabited homes, one species is generally the most prevalent, but the dominant species varies between homes and also between geographic areas.

Because of their cosmopolitan occurrence and the varied patient exposure to multiple species, this ecologic information is of clinical importance in evaluating patients and also in selecting or assessing effective immunotherapy.

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Venom Immunotherapy

IN THE TEN YEARS since the Food and Drug Administration approved immunotherapy with venoms and venom sac extracts as the treatment of choice for stinging insect hypersensitivity, many groups have reported that only 3% to 5% of venom-treated patients have systemic allergic reactions with subsequent stings, compared with 60% of untreated adults. By contrast, children whose reactions, including urticaria and angioedema, have been confined to the skin appear to have only about a 10% risk of a reaction if stung without immunization; most of those children who do have a reaction when stung have reactions no worse than their original one. A summary of indications for venom immunotherapy includes any systemic manifestation of hypersensitivity in an adult, any extracutaneous manifestation of systemic reactivity in a child, and positive skin tests or radioallergosorbent tests to venom(s).

The success of immunotherapy is judged by the failure to react systemically to a challenge sting. Because the risk of failure of therapy is so small, some authorities think that routine monitoring of venom-specific immunoglobulin (Ig) G antibody levels (whose rise is associated with the appearance of immunity to sting reactions) is unnecessary. Nevertheless, the risk of treatment failure when the antivenom IgG level is less than 0.003 grams per liter is 16%, compared with 3% in patients with IgG values greater than 0.003 grams per liter. When necessary, IgG levels can often be increased by increasing the venom dose to 200 μg per injection of each relevant venom or increasing the frequency of injections.

It is still unknown how long venom immunotherapy should be continued. A high antivenom IgG value is not a sufficient cause for discontinuing venom immunotherapy because the IgG level will fall after therapy is stopped. If treatment is stopped after two years or less of therapy, the risk of reactions to stings rises to about 25% to 30%. One research center reported that after five or more years of uninterrupted venom immunotherapy, the risk of a systemic reaction to sting challenge one, two, and three years after stopping therapy is small. This has been true regardless of whether skin tests are positive or negative and regardless of the titers of venom-specific IgE or IgG at that point. Even so, the risk of future resensitization is unknown. Before these findings can be generally accepted as guidelines for terminating therapy, the long-term sequelae of stopping venom treatment must be understood.

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Autoimmune Demyelinating Disease

MULTIPLE SCLEROSIS is a demyelinating disease of the central nervous system affecting approximately 250,000 Americans. Although the clinical manifestations are protean, classic features include relapsing or chronic unremitting paralysis. The histologic hallmark is focal areas of demyelination (plaques) within the white matter of the brain and spinal cord. Several lines of evidence indicate that multiple sclerosis is an autoimmune disorder. As with many autoimmune diseases, a susceptibility to multiple sclerosis is associated with certain HLA-D genes—immune response genes that encode the class II molecules of the major histocompatibility complex. These molecules are necessary for antigen recognition by CD4+ lymphocytes. Investigators have found an increased number of class II-bearing cells and a predominance of CD4+ T cells in demyelinating multiple sclerosis lesions.

Experimental allergic encephalomyelitis (EAE) is the prototypic model for autoimmune demyelinating disease. It occurs in certain strains of mice and other mammalian species following immunization with the autoantigen myelin basic protein (MBP), the major constituent of central nervous system myelin. Experimental allergic encephalomyelitis can also be induced by adoptive transfer of MBP-specific CD4+ T cells into naive recipient mice. As with multiple sclerosis, susceptibility to EAE is associated with certain class II genes of the major histocompatibility complex, and antibodies to these molecules can prevent EAE. Further, a predominance of class II-bearing cells and CD4+ T cells is found in the demyelinating lesions of EAE. Individual MBP-specific CD4+ T-cell clones that are class II restricted have been isolated that mediate EAE. These T cells are all descendants from a single clone that causes chronic relapsing paralysis and demyelination. The identification of these clones allowed us to characterize the T cells involved in autoimmune demyelination and to further elucidate the role of the major histocompatibility complex. We found that a limited number of MBP-specific CD4+ T cells cause EAE, and it has been reversed with antibodies to the antigen-specific receptors on these T cells. As in patients with EAE, T cells bearing a restricted number of T-cell receptors have been found in the brain and cerebrospinal fluid of patients with multiple sclerosis.

Contemporary therapies for multiple sclerosis focus on modalities that have been effective in other autoimmune dis-

eases. The use of cyclophosphamide, total lymphoid irradiation, and the use of synthetic copolymers are all promising experimental approaches to the treatment of multiple sclerosis. Therapy with monoclonal antibodies directed against specific T-cell subsets and T-cell receptors holds promise.

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Spacers and Reservoirs in Delivery Systems

SPACERS AND RESERVOIRS were developed to aid the delivery of drugs from metered-dose inhalers. These devices, which are attached to the inhalers, should hold the aerosolized spray, making synchronizing between a metered-dose inhaler actuation and inhalation less critical; allow aerosolized droplets to evaporate to a fine mist, delivering the maximal amount of drug to the lungs; and decrease oropharyngeal deposition. β-Adrenergic agonists delivered by metered-dose inhalers in doses of as much as six times those normally recommended, with or without a spacer, give bronchodilation equivalent to nebulizers in patients with acute and chronic asthma, except in some patients with severe asthma.

Delivery to the lung of a whiff by a metered-dose inhaler—at most 15% of each dose—can be improved by holding the inhaler 3 to 4 cm from a wide-open mouth (some authorities prefer the lips to be closed around the mouthpiece), triggering the inhaler during a slow, deep inhalation over five seconds followed by a ten-second breath-hold. Spacers help improve delivery of a drug in a third to half of those patients who cannot correctly use a metered-dose inhaler but add little further therapeutic effect in patients using a proper inhaler technique.

With β-adrenergic agonists, larger spacers with a volume of 750 ml improve bronchodilator response more than smaller spacers. Five spacers are currently available in the United States: Brethancer (Geigy) and Azmacort (Rorer Pharmaceuticals) tube spacers (80 ml and about 100 ml volume) are specifically for terbutaline and triamcinolone metered-dose inhalers; universal add-on devices available are the AeroChamber (Forest Pharmaceuticals), a rigid tube (145 ml); InspirEase (Key Pharmaceuticals), a collapsible bag; and Inhal-Aid (Key Pharmaceuticals), a rigid reservoir (both 700 ml). Other spacers with a pear or cone shape, with about a 750-ml volume and for which there are favorable studies, are not available at present.

Studies with β-adrenergic agonists using Brethancer, AeroChamber, and InspirEase show considerable variation in the effectiveness of these devices relative to a metered-dose inhaler alone. Children using isoproterenol in a metered-dose inhaler with Inhal-Aid achieve bronchodilation equal to that with the use of isoproterenol by intermittent positive pressure breathing. The Azmacort tube spacer, InspirEase, AeroChamber, and Brethancer decrease oropharyngeal deposition, and the latter two have been shown to decrease oropharyngeal thrush from inhaled steroids. AeroChamber has been shown to decrease the dysphonia from inhaled beclomethasone dipropionate.

Physicians should have patients demonstrate their inhaler technique. If it is inadequate or if oropharyngeal thrush or dysphonia from inhaled steroids is a problem, then a spacer, used properly, may be of benefit.

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Methacholine Inhalation Challenge for Diagnosis of Asthma

ASTHMA IS RECOGNIZED CLINICALLY by reversible airway obstruction and airways hyperreactivity. Since the 1940s, bronchial inhalation challenges with pharmacologic and antigenic substances have been used to detect airway hyperreactivity. Bronchoconstriction in patients with asthma can be induced by methacholine, acetylcholine, histamine, carbachol, pilocarpine, serotonin, propranolol, methoxamine, adenosine, prostaglandin D_2 or $F_{2\alpha}$, and leukotrienes C_4 and D_4. Of these, methacholine chloride (Provocholine [Hoffmann La Roche]) has recently been approved by the Food and Drug Administration for inhalation to identify the presence of bronchial hyperreactivity. Methylcholine, a β-methyl homologue of acetylcholine, stimulates the muscarinic receptors on bronchial smooth muscle, increasing bronchomotor activity. Although airways hyperreactivity is present in asthma, the diagnosis is generally made from a combination of history, physical examination findings, and the results of spirometry. Methacholine inhalation challenge is indicated only when the usual evaluation is not diagnostic, such as with patients who have vague symptoms or symptoms such as cough, episodic chest tightness, or atypical dyspnea with normal physical findings and spirometric values. Bronchial challenge may also be used to identify workers who are at risk of occupational asthma developing because of preexisting bronchial hyperresponsiveness. As a research tool, bronchial challenges help clarify the mechanisms of asthma and evaluate new drugs.

Standard procedures for inhaling methacholine have been developed. Factors that influence the response to challenge, such as viral or bacterial respiratory tract infections and pollutants, should be avoided. Various drugs influence the outcome of a challenge, including bronchodilators, cromolyn sodium, and antihistamines. To be challenged, a person should have a baseline forced expiratory volume in one second (FEV_1) of at least 70% of the predicted value. Challenge is done by diluting methacholine from a dry powder and having the patient inhale aerosolized methacholine in ascending concentrations ranging from 0.025 mg per ml of methacholine to 25 mg per ml. Two methods of inhalation are used: five breaths are inhaled from a DeVilbiss nebulizer 646 with a Rosenthal-French dosimeter (0.65 delivery time); or 3 ml of methacholine solution are placed in a